SAC

Atty. Dkt. No. 038602-0297 9200/642

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#9

Applicant: Annie FONG et al.

Title: METHOD OF DETERMINING AN EFFICACIOUS DOSE OF A DRUG

Appl. No.: 09/186,475

Filing Date: 11/04/1998

Examiner: Susan Ungar

Art Unit: 1642

PETITION UNDER 37 C.F.R. §1.181(a) TO WITHDRAW IMPROPER HOLDING OF ABANDONMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The Assistant Commissioner for Patents is hereby petitioned to withdraw the holding of abandonment that was issued in error on February 26, 2003, in the application identified above. The holding of abandonment was made in error because, as explained below, a Reply to the May 21, 2002, Office Action was timely filed on November 21, 2002.

On May 21, 2002, a Final Rejection was mailed setting a shortened statutory period for response of three (3) months. A copy is enclosed as Exhibit A.

On November 21, 2002, Applicants filed (a) an After-Final Amendment, (b) a Notice of Appeal and (c) a Petition for a 3-Month Extension of Time. Copies of all documents filed as well as the date-stamped post card are enclosed as Exhibit B.

On January 28, 2003, an Advisory Action was mailed indicating that the Appellants' Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof to avoid dismissal of the appeal. A copy is enclosed as Exhibit C.

On February 26, 2003, a Notice of Abandonment was mailed indicating that Applicants had failed to respond to the May 21, 2002, Office Action. A copy is enclosed as Exhibit D.

In view of these circumstances, the Commissioner is petitioned for an order withdrawing the notice of abandonment and returning the application to pending status for further action on the merits.

No fee is due with respect to this petition (MPEP §711.03(c)(I)).

Respectfully submitted,

Date 3/19/03

By _____

Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

FOLEY & LARDNER
Customer Number: 22428

22428
PATENT TRADEMARK OFFICE
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,475	11/04/1998	ANNIE FONG	238/046	1830

7590 05/21/2002

BETH A. BURROUS
FOLEY & LARDNER WASHINGTON HARBOUR
3000 K STREET, N.W., SUITE 500
WASHINGTON, DC 20007-5109

EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/186,475	Fong et al.
Examiner	**Art Unit**
Jennifer Hunt	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 26, 2002*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11, 15-21, 23, 24, and 27-32* is/are pending in the application.

4a) Of the above, claim(s) *19-21, 27, and 32* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11, 15-18, 23, 24, and 28-31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. Acknowledgment is made of applicant's cancellation of claim 22, and further applicant's cancellation of the previously effect species of "protein phosphorylation" from generic claim 1. The search was extended with regard to species E "angiogenesis markers" and u-PA was found in the prior art, and thus the claims have been considered only to the extent that they encompass uPA. It is noted that claim 15 needs to be updated with regard to the amendments of claim 1. Claims 1-11, 15-21, 23-24, and 27-32 are pending in the application. Claims 19-21, 27, and 32 have been withdrawn from consideration as being drawn to a non-elected species of invention. An action on the merits of claims 1-11, 15-18, 23-24, and 28-31 follows herein.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Claim Rejections Withdrawn

3. The rejections of claims 1-11, 15-18, 23-24, and 28-31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in light of the amendments thereto.

Claim Rejections Maintained

4. The grounds of rejection of claims 1-11, 15-18, 23-24, and 28-31 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monitoring markers known in the art to correlate to angiogenesis for the purpose of determining an effective dose of an angiogenesis inhibitor, does not reasonably provide enablement for monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL-8, and t-PA, for the purpose of determine an effective dose of an angiogenesis modulator. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to a method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis comprising administering the compound to a patient, monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL-8, and t-PA, constructing a standard curve, and determining the efficacious dose based on the standard curve.

The specification provides generalized theoretical teachings in which a limited number of markers (tissue factor, IL-8, urokinase and tPA) are measured using PCR or ELISA, and a

standard curve is generated to determine how much of the marker is in the isolated sample after a patients have received some sort of unspecified drug treatment. In a second theoretical example, cells are isolated from a patient, then administered a Flk-1 antagonist *in vitro*, and then the cells are eventually lysed and a marker is measured.

Thus the specification fails to provide any guidance or objective evidence that any of the markers which are taught or suggested by the specification in fact correlate to angiogenesis.

Diagnosing and monitoring cancer is an extremely complex process. Often a single factor (such as monitoring a marker) is insufficient to provide an accurate assessment of tumor progress or regression. Further, often a single variable will provide some information about a primary tumor, but fail to provide information regarding metastasis. If the treatment efficacy of a drug is to be measured using a marker, that marker must be carefully selected to be specific and accurate for the determination of the treatment's efficacy. Determination of a dosage using such a marker is even more complex. The marker which is selected must be known to specifically correlate to the progression or regression of disease, taking into account not only tumor size, metastasis, aggressiveness, etc., but also toxicity, quality of life of the patient, etc. (For general guidelines on some of the factors for determining drug dosage, see pages 33-37 of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I). In the instant case, the method fails to account for any of these factors. Further there is no guidance or objective evidence that the broadly recited markers correlate to progression or regression of any cancer, and thus there is no correlation of the broad range of markers to any type of cancer. Further, the most relevant

example provided by the specification (that of a Flk-1 antagonist) refers to an *in vitro* test, which never involves administration of any compound to a patient. Thus it is not clear from applicant's teachings or examples that any marker correlates accurately enough to cancer progression such that it would be effective for determine a dosage curve for a patient.

Thus the claims are broadly drawn, encompassing any one of 6 markers, with no evidence that they would actually correlate to "angiogenesis modulation", particularly in vivo. The state of the art of drug dosage and determination is complex and unpredictable, with many factors which complicate the effective determination of a dose. Therefor one of skill in the art would not be enabled to practice the invention commensurate in scope with the claims.

Applicant agues that the amendments to the claims overcome the grounds of rejection. Applicant's arguments filed 2-26-2002 have been fully considered but are not persuasive.

As set forth above, the specification fails to provide guidance or objective evidence that one of skill in the art would be enabled to use the invention commensurate in scope with the claims.

New Grounds of Rejection

5. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites the limitation "wherein the marker is selected from the group consisting of cell division, cell mortality, cell proliferation, cell death, cell survival, cell differentiation, protein phosphorylation, protein expression, protein glycosylation, mRNA expression, cellular membrane potentia, DNA division, DNA methylation, and post-translational modification.." There is insufficient antecedent basis for this limitation in the claim.

6. Claims 1-6, 9-11, 15-18, 23-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al., US Patent 6,177,401, published January 23, 2001, in view of Hirth, US Patent 5,942,385, and in view of Mandriota et al., The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716, April 1997 (IDS), and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 6,177,401 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, including angiogenesis related to cell proliferation (cancer), specifically the Flk-1 (a receptor involved in angiogenesis) antagonists, comprising administering the compound to a patient, monitoring a marker related to angiogenesis (including protein phosphorylation, or a protein which is expressed in correlation to VEGF), including comparing the marker to a standard, using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 12, line 54-column 16, line 39, column 29, line 49-column 30, line 25, and column 23, lines 30-56).

US Patent 6,177,401 fails to teach a the administration of this monitoring assay to a patient, that the protein which is expressed in correlation to VEGF is uPA, and determination of a correct drug dose using a standard curve.

US Patent 5,942,385 teaches that VEGF and flk-1 can be used to monitor cancer in patients, including in patients blood (which would inherently include monocytes) (see for example, column 6, lines 34-67).

Mandriota et al. teaches that uPA is increased in blood cells in response to VEGF. (Page 9710, column 1.)

Fingl and Woodbury teaches methods of determine efficacious drug dosages, including generating a standard curve.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure flk-1 activity (including protein phosphorylation, or a protein which is expressed in correlation to VEGF), and further use uPA to measure angiogenesis, and further calculate a drug dose using the drug dosage standard curve of Fingl and Woodbury, and one would have been motivated to do so because flk-1 activity (including uPA, a protein which is expressed in correlation to VEGF) correlates to drug efficacy, as taught in 6,177,401, and can be easily measured in numerous body fluids, including blood, as taught in 5,942,385, and because the dosage standard curves were the art standard way of determine an appropriate drug dose.

7. Claims 1-11, 15-18, 23-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al., US Patent 5,792,783, published August 11, 1998, in view of Hirth, US Patent 5,942,385, and in view of Mandriota et al., The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716, April 1997 (IDS), and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 5,792,783 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, including angiogenesis related to cell proliferation (cancer), specifically the Flk-1 (a receptor involved in angiogenesis) antagonist SU 5416 (which is the instant compound a of claim 8), comprising administering the compound to a patient, monitoring a marker related to angiogenesis (protein phosphorylation or expression of a VEGF related protein) using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 2, line 63-column 3, line 40, column 13, lines 5-line 37, column 17, line 65-column 18, line 60, column 22, lines 59-67, and column 32, line 32-column 34, line 44).

US Patent 5,792,783 fails to teach a the administration of this monitoring assay to a patient, including measurement of u-PA, and determination of a correct drug dose using a standard curve.

US Patent 5,942,385 teaches that VEGF and flk-1 can be used to monitor cancer in patients, including in patients blood (which would inherently include monocytes) (see for example, column 6, lines 34-67).

Mandriota et al. teaches that u-PA is increased in blood cells in response to VEGF. (Page 9710, column 1.)

Fingl and Woodbury teaches methods of determine efficacious drug dosages, including generating a standard curve.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure flk-1 activity (including measuring protein phosphorylation or measuring u-PA which correlates to VEGF), and further calculate a drug dose using the drug dosage standard curve of Fingl and Woodbury, and one would have been motivated to do so because flk-1 activity (including protein phosphorylation and u-PA activity) correlates to drug efficacy, as taught in 5,792,783, and can be easily measured in numerous body fluids, including blood, as taught in 5,942,385, and because the dosage standard curves were the art standard way of determine an appropriate drug dose.

8. Claims 1-11, 15-18, 23-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al., US Patent 6,177,401, published January 23, 2001, in view of Hirth, US Patent 5,942,385, and in view of Mandriota et al., The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716, April 1997 (IDS), and further in view of Tang et al., US Patent 5,792,783, published August 11, 1998, and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 6,177,401 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, including angiogenesis related to cell proliferation (cancer), specifically the Flk-1 (a receptor involved in angiogenesis) antagonists, comprising administering the compound to a patient, monitoring a marker related to angiogenesis (including measuring a protein which is expressed in correlation to VEGF, or protein phosphorylation) using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 12, line 54-column 16, line 39, column 29, line 49-column 30, line 25, and column 23, lines 30-56).

US Patent 6,177,401 fails to teach administration of this monitoring assay to a patient, the specific Flk-1 antagonist SU 5416, and determination of a correct drug dose using a standard curve.

US Patent 5,942,385 teaches that VEGF and flk-1 can be used to monitor cancer in patients, including in patients blood (which would inherently include monocytes) (see for example, column 6, lines 34-67).

Mandriota et al. teaches that u-PA is increased in blood cells in response to VEGF. (Page 9710, column 1.)

US Patent 5,792,783 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, specifically the Flk-1 antagonist SU 5416 (which is the instant compound a of claim 8), comprising administering the compound to a patient,

monitoring a marker related to angiogenesis (protein phosphorylation) using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 2, line 63-column 3, line 40, column 13, lines 5-line 37, column 17, line 65-column 18, line 60, column 22, lines 59-67, and column 32, line 32-column 34, line 44).

Fingl and Woodbury teaches methods of determine efficacious drug dosages, including generating a standard curve.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the specific Flk-1 antagonist of US Patent 5,792,783, or the drug dosage standard curve of Fingl and Woodbury with the dosage assay of US Patent 6,177,401, and one would have been motivated to do so because the drug SU 5416 is a known Flk-1 antagonist, as taught by US 5,792,783, and because the dosage standard curves were the art standard way of determine an appropriate drug dose. Further one would have been motivated to administer such to a patient because flk-1 activity (including protein phosphorylation or u-PA activity) correlates to drug efficacy, as taught in 5,792,783.

9. Claims 1-11, 15-18, 23-24, and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al., US Patent 6,177,401, published January 23, 2001, in view of Hirth, US Patent 5,942,385, and in view of Mandriota et al., The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716, April 1997 (IDS), and further in view of Tang et

al., US Patent 5,792,783, published August 11, 1998, and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 6,177,401, US Patent 5,792,783, Mandriota et al., US Patent 5,942,385, and Fingl and Woobury teach as set forth supra. US Patent 6,177,401, US Patent 5,792,783, Mandriota et al., US Patent 5,942,385, and Fingl and Woobury fail to teach that the specific efficacious dosages and standard curves.

Determination of specific optimal standard dosages/standard curves represents optimization of the known dosage curve methods and would be a matter of routine experimentation, given what is known in the art, exemplified in US Patent 6,177,401, US Patent 5,792,783, Mandriota et al., US Patent 5,942,385, and Fingl and Woobury.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was alter the methods of US Patent 6,177,401, US Patent 5,792,783, Mandriota et al., US Patent 5,942,385, and Fingl and Woobury to generate the specific standard curves of the instant claims and one would have done so as means of determining the most effective dose, based on the teachings and knowledge in the prior art.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

May 20, 2002

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER

FOLEY & LARDNER

30

038602/0297

Receipt is hereby acknowledged of the following:

APPLICANT: **Annie FONG, et al.**
SERIAL NO: **09/186,475** Examiner: **J. Hung**
FILING DATE: **11/04/1998** Art Unit: **1642**
FOR: ***Method of Determining an Efficacious Dose of a Drug***

Receipt is hereby acknowledged of the accompanying:

- Amendment
- Petition for Three Month Extension of Time
- Notice of Appeal
- Check # 25164 for $1,240.00 (3 EOT, Notice of Appeal)

Date Due: November 21, 2002
Date Filed: November 21, 2002

Return to: BAB/PDS:ljp
Insp. By

Atty. Dkt. No 038602-0297

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Annie FONG et al.

Title: METHOD OF DETERMINING AN EFFICACIOUS DOSE OF A DRUG

Appl. No.: 09/186,475

Filing Date: 11/04/1998

Examiner: J. Hunt

Art Unit: 1642

PETITION FOR EXTENSION OF TIME

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant hereby petitions the Commissioner under 37 C.F.R. §1.136(a) for a three-month extension of time for response in the above-identified application for the period required to make the attached response timely.

The extension fee for response within the third month is $920.00. A check for this amount is enclosed herewith.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date 11/21/02

By _____

Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

FOLEY & LARDNER
Customer Number: 22428
22428
PATENT TRADEMARK OFFICE
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

Atty. Dkt. No. 038602-0297

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Annie FONG et al.

Title: METHOD OF DETERMINING AN EFFICACIOUS DOSE OF A DRUG

Appl. No.: 09/186,475

Filing Date: 11/04/1998

Examiner: J. Hunt

Art Unit: 1642

NOTICE OF APPEAL FROM THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant hereby appeals to the Board of Patent Appeals from the decision of the final rejection dated May 21, 2002, and the Advisory Action dated , of the Examiner finally rejecting Claims 1-11, 15-18, 23, 24 and 27-32.

[ ] Applicant claims small entity status.

[X] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[X] Notice of Appeal Fee

[X]To be paid as detailed below

[ ]Not required (Fee paid in prior appeal)

The required fees are calculated below:

[X]	Notice of Appeal Fee	$320.00
[X]	Extension for response filed within the third month:	$920.00
[ ]	Extension:	$0.00
	FEE TOTAL:	$1240.00
[ ]	Small Entity Fees Apply (subtract ½ of above):	$0.00
	TOTAL FEE:	$1240.00

[ ] Please charge Deposit Account No. 19-0741 in the amount of $1240.00 . A duplicate copy of this transmittal is enclosed.

[X] A check in the amount of $1240.00 is enclosed.

[X] The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date 11/21/02

By _____

FOLEY & LARDNER
Customer Number: 22428

22428
PATENT TRADEMARK OFFICE
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

Atty. Dkt. No. 038602-0297

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Annie FONG et al.

Title: METHOD OF DETERMINING AN EFFICACIOUS DOSE OF A DRUG

Appl. No.: 09/186,475

Filing Date: 11/04/1998

Examiner: J. Hunt

Art Unit: 1642

AMENDMENT AND RESPONSE UNDER 37 C.F.R. §1.116

Commissioner for Patents
Box AF
Washington, D.C. 20231

Sir:

This communication is responsive to the Office Action dated May 21, 2002, concerning the above-referenced patent application.

Applicant has enclosed with this amendment a Petition for Extension of Time to make this response timely. The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please amend the application as follows:

In the Claims:

Please cancel claim 15 without prejudice or disclaimer.

REMARKS

Applicants acknowledge receipt of an Office Action dated May 21, 2002. In this response, Applicants have cancelled claim 15 without prejudice or disclaimer. Following entry of this amendment, claims 1-11, 15-21, 23, 24 and 27-32 are pending in the application. The Examiner has withdrawn claims 19-21, 27 and 32 from consideration as being drawn to non-elected subject matter.

Reconsideration of the present application is respectfully requested in view of the foregoing amendments and the remarks which follow.

Rejections Under 35 U.S.C. §112, 2nd Paragraph

On page 5 of the Office Action, the Examiner has rejected claim 15 under 35 U.S.C. §112, 2nd paragraph as allegedly being indefinite. In this response, Applicants have cancelled claim 15 without prejudice or disclaimer. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections under 35 U.S.C. §112, 2nd paragraph.

Rejections Under 35 U.S.C. §112, 1st Paragraph

On page 3 of the Office Action, the Examiner has rejected claims 1-11, 15-18, 23-24 and 28-31 under 35 U.S.C. §112, 1st paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants respectfully traverse this rejection for the reasons set forth below.

In the Office Action, the Examiner states that the specification, while being enabling for monitoring markers known in the art to correlate to angiogenesis for the purpose of determining an effective dose of an angiogenesis inhibitor, does not reasonably provide enablement for monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL-8, and t-PA, for the purpose of determining an effective dose of an angiogenesis modulator. On page 4 of the Office Action, the Examiner states that "the specification fails to provide any guidance or objective evidence that any of the markers which are taught or suggested by the specification in fact correlate to angiogenesis." The Examiner continues, on page 5, arguing that "[t]he state of the art of drug dosage determination is complex and unpredictable, with many factors which complicate the effective determination of a dose" and concludes that "one skilled in the art would not be enabled to practice the

invention commensurate in scope with the claims." Applicants submit that the Examiner has failed to establish a proper basis for rejection under 35 U.S.C. §112, 1st paragraph.

Applicants submit that the markers recited in present claim 1 (tissue factor, CD40, u-PA, ETS-1, IL-8, and t-PA) is enabled within the disclosure of the present application. The Examiner's attention is directed to information in the instant specification which provides enabling support for these markers. Specifically, the Examiner's attention is directed to the description on pages 23-26 of the specification, particularly the discussion under the heading "IV. Other Markers" on pages 24 and 25.

With regard to whether the claimed markers correlate to angiogenesis, Applicants respectfully disagree with the Examiner's position and submit that the Examiner has failed to come forward with objective evidence of non-enablement and has thereby improperly shifted her burden to Applicants.

As discussed *supra*, Applicants have stated, in the specification, that the claimed markers correlate to angiogenesis. It is well settled law that the Applicants' specification is considered presumptively accurate and enabling, absent contrary evidence presented. *In re Wright*, 27 USPQ2d 1510 (Fed Cir. 1993). Indeed, as stated by the court in *In re Marzocchi*,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 223. Thus, Applicants enjoy a presumption of enablement, and a failure to rebut this presumption means that their specification is enabling as a matter of law.

The present Office Action, rather than recognizing Applicants' presumption, improperly shifts the burden to Applicants to positively prove enablement. Clearly, such a burden shift is not proper under the law. Absent a clear showing by the Examiner as to why these markers do not correlate with angiogenesis, Applicants specification is fully enabled.

Finally the Examiner's statement that "the art of drug dosage and determination is complex and unpredictable" is merely conclusory. Applicants contend that, in view of

the foregoing, this argument of unpredictability is not sufficient to meet the requirement for a *prima facie* establishment of lack of enablement.

In *Wands*, the Federal Circuit indicated that

> [i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole.

Id., at 737, 740. Moreover, the critical inquiry is whether any experimentation is required is undue. The Examiner has not demonstrated that it would require undue experimentation to practice the claimed invention. "Enablement . . . is not precluded even if some experimentation is necessary." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections under §112, 1st paragraph.

Rejections Under 35 U.S.C. §103

In the Office Action, the Examiner has set forth 4 different rejections under 35 U.S.C. §103. Specifically:

- On page 6 of the Office Action, the Examiner has rejected claims 1-6, 9-11, 15-18 and 23-24 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 6,177,401 to Ullrich *et al.* (hereafter "Ullrich") in view of U.S. Patent 5,942,385 to Hirth (hereafter "Hirth") in view of The Journal of Biological Chemistry, Vol. 270, No. 17, pages 9709-9716 (hereafter "Mandriota") and further in view of Fingl and Woodbury, The Pharmacological Basis of Therapeutics, Chapter 1, pages 25-33 (hereafter "Fingl and Woodbury").
- On page 8 of the Office Action, the Examiner has rejected claims 1-11, 15-18, 23-24 and 28 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 5,792,783 to Tang *et al.* (hereafter "Tang") in view of Hirth in view of Mandriota, and Fingl and Woodbury.
- On page 9 of the Office Action, the Examiner has rejected claims 1-11, 15-18, 23-24 and 28 under 35 U.S.C. §103(a) as being unpatentable over Ullrich in view of Hirth in view of Mandriota in view of Tang and further in view of Fingl and Woodbury.

- On page 11 of the Office Action, the Examiner has rejected claims 1-11, 15-18, 23-24 and 28-31 under 35 U.S.C. §103(a) as being unpatentable over Ullrich in view of Hirth in view of Mandriota in view of Tang and further in view of Fingl and Woodbury.

Applicants respectfully traverse each of these rejections for the reasons set forth below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143.

Here, in each of the rejections set forth in the Office Action, the Examiner has failed to establish either (1) a proper motivation to combine the references or (2) a reasonable expectation of success. Specifically, Applicants submit that the Examiner has failed to establish a proper motivation to combine either of the two primary references, Ullrich and Tang, which each relate to Flk-1 and VEGF with Mandriota which relates to u-PA. Applicants further submit that the Examiner has failed provide a basis for a reasonable expectation of success based on the combination of the references. Applicants also note that each of the rejections has required at least 4 references. At best, the PTO, using Applicants disclosure as a blueprint, appears to have selectively chosen bits and pieces of the prior art that were otherwise unrelated to arrive at the presently claimed invention. It is well settled that the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. MPEP §2141.

Applicants further note that Ullrich fails to teach or fairly suggest monitoring markers and, further, fails to teach or fairly suggest monitoring of u-PA. While Mandriota discloses that u-PA increases with VEGF, this reference fails to disclose a method of determining an efficacious does of a compound administered to a subject for the purpose of modulating angiogenesis comprising monitoring u-PA. As the other cited

references fails to cure these deficiencies, Applicants submit that none of the cited references, taken either individually or in combination, teach or properly suggest the inventions set forth in pending claim 1.

If an independent claim is nonobvious under §103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03. Thus, Applicants submit that claims 2-11, 15-18, 23, 24 and 28-31, which depend directly or indirectly independent claim 1, are also non-obvious.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

Respectfully submitted,

Date 11/21/02

By _____

FOLEY & LARDNER
Customer Number: 22428
22428
22428
PATENT TRADEMARK OFFICE
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,475		ANNIE FONG	238/046	1830

7590 01/28/2003

BETH A. BURROUS
FOLEY & LARDNER WASHINGTON HARBOUR
3000 K STREET, N.W., SUITE 500
WASHINGTON, DC 20007-5109

EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/28/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/186,475	Fong et al
Examiner	**Art Unit**
Ungar	1642

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

THE REPLY FILED *Nov 21, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Oct 1, 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s): _____

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*

Claim(s) objected to: *none*

Claim(s) rejected: *1-3, 5-11, 16-18, 23, 24, and 28-31*

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

10. ☐ Other:

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

1. The Amendment-After-Final filed November 21, 2002 (Paper No. 16) in response to the Office Action of May 21, 2002 (Paper No. 14) is acknowledged and has been entered. Previously pending claim 15 has been canceled.

Claim Rejections - 35 USC § 112

2. Claims 1-3, 5-11, 16-18, 23-24, 28-31 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 14, Section 4, pages 3-5.

Applicant argues that (a) the markers recited in present claim 1 is enabled within the disclosure of the present application wherein the Examiner's attention is directed to the description on pages 23-26, in particular pages 24-25 drawn to other markers, (b) Applicant cites case law, *In re Wright, In re Marzocchi, Hybritech Inc. V. Monoclonal Antibodies, Inc.*, and argues that the Office improperly shifts the burden to Applicants to positively prove enablement rather than recognizing Applicants' presumption of enablement and that undue experimentation is not required to practice the claimed invention.

The arguments have been considered but have not been found persuasive because (a') a review of the cited support shows that the support is rife with uncertainties, for example, p. 24, line 24 "CD40 may be related to angiogenesis", p. 24, line 25 "suggest a role for the plasminogen activation system in tumoral angiogenesis". Further, p. 25, lines 9-14 are drawn to t-PA which is released from endothelial cells and whose high expression level correlates with poor outcome, there is not even a suggestion that the marker is associated with angiogenesis. Although the specification states that ETS-1 regulates the expression of certain

genes and that it plays an important role in angiogenesis apparently because it regulates the expression of proteases, it does not appear that a direct correlation to angiogenesis such that its expression can be used as specifically claimed, has been established for the reasons of record, (b) Examiner presented sound scientific reasoning as well as published guidelines on factors for determining drug dosage. Although Applicant cites support in the specification and cites case-law, it is noted that Applicant does not argue that Examiner is incorrect in the finding that the invention is not enabled because the specification fails to provide any guidance or objective evidence that any of the markers which are taught or suggested by the specification in fact correlate with angiogenesis of that the state of the art is complex and unpredictable. Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

3. Claims 1-3, 5-6, 9-11, 16-18, 23-24 remain rejected under 35 USC 103 first paragraph for the reasons previously set forth in Paper No. 14, Section 6, pages 6-7.

Claims 1-3, 5-11, 16-18, 23-24, 28 remain rejected under 35 USC 103 first paragraph for the reasons previously set forth in Paper No. 14, Section 7, pages 8-9.

Claims 1-3, 5-11, 16-18, 23-24, 28 remain rejected under 35 USC 103 first paragraph for the reasons previously set forth in Paper No. 14, Section 8, pages 9-11.

Claims 1-3, 5-11, 16-18, 23-24, 28-31 remain rejected under 35 USC 103 first paragraph for the reasons previously set forth in Paper No. 14, Section 9, pages 11-12.

Since Applicant argues all of the rejections under 35 USC 103 first paragraph together, the response to all of the rejections will likewise be done.

Applicant argues that (a) Applicant has failed to establish proper motivation or a reasonable expectation of success. The argument is drawn in particular, Ullrich and Tang, each of which relate to FLK-1 and VEGF and Mandriota which relates to u-PA wherein Examiner has failed to establish a proper motivation to combine or provided a bases for a reasonable expectation of success, (b) Examiner relies on at least four references, at best using Applicant's disclosure as a blueprint and therefore using impermissible hindsight vision, (c) Ullrich fails to teach or fairly suggest monitoring markers or suggest monitoring of u-PA, while Mandriota discloses u-PA increases with VEGF, this reference fails to disclose a method of determining an efficacious dose to a subject for the purpose of modulating angiogenesis comprising monitoring u-PA and the other references fail to cure these deficiencies.

The arguments have been considered but have not been found persuasive because (a') as previously set forth, Tang et al specifically teach a method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis, as previously set forth Ullrich teaches known markers (VEGF and flk-1) used to monitor cancer in patients wherein, as taught by Mandriota, u-PA is increased in blood cells in response to VEGF. Examiner provides a nexus between the known markers and u-PA and clearly provides motivation for the combination for the reasons previously set forth, (b') in response to applicant's argument that the examiner's conclusion of obviousness is based upon

improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981), (c')Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981). Applicant's arguments have not been found persuasive and the rejection is maintained.

SUSAN [illegible], PH.D
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,475	11/04/1998	ANNIE FONG	238/046	1830

7590 02/26/2003

BETH A. BURROUS
FOLEY & LARDNER WASHINGTON HARBOUR
3000 K STREET, N.W., SUITE 500
WASHINGTON, DC 20007-5109

EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Notice of Abandonment

Application No.	Applicant(s)
09/186,475	Fong et al
Examiner	**Art Unit**
Ungar	1642

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *May 21, 2002* .

   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of ____ month(s)) which expired on _____ .

   (b) ☒ A proposed reply was received on *Nov 21, 2002* , but it does not constitute a proper reply under 37 CFR 1.113(a) to the final rejection.

   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).

   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).

   (d) ☐ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).

   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).

   (b) ☐ The submitted issue fee of $_____ is insufficient. A balance of $_____ is due.

   The issue fee required by 37 CFR 1.18 is $_____ . The publication fee, if required by 37 CFR 1.18(d) is $_____

   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).

   (a) ☐ Proposed new formal drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.

   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interferences rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.